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APPLICANT : SAGAMI CHEM RES CENTER;

INVENTOR : YAMADA KAORU;

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TITLE : CALCIUM CHANNEL ANTAGONIST

ABSTRACT : PROBLEM TO BE SOLVED: To obtain the subject new antagonist inhibiting inflow of calcium to cell by using an extract of salivary gland of shrew as an active ingredient.

SOLUTION: This antagonist contains an extract of salivary gland of shrew as an active ingredient. An insectivore such as Sorex unguiculatus Dobson or Sorex shinto saevus Thomas is exemplified as the shrew. A lower alcohol such as ethanol or ketone such as acetone is exemplified as organic solvent used for extraction. When an auxiliary for production such as excipient and disintegrator is used, formulating amount of an extract of salivary gland is preferably 0.2-10wt.%. The daily dose of the extract is preferably 1-1,000mg when an adult is treated as the concentrate of the extract and the extract is preferably administered in 2-3 divided portions.

George et al. 1986.

MAMMALIAN SPECIES No. 261, pp. 1–9, 3 figs.

Blarina brevicauda.

By Sarah B. George, Jerry R. Choate, and Hugh H. Genoways

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Blarina Gray, 1838

Blarina Gray, 1838:124. Type species *Corsira* (*Blarina*) *talpoides* Gray (=*Sorex talpoides* Gapper = *Sorex brevicaudus* Say), by original designation. Elevated to generic rank by Lesson, 1842:89.

Brachysorex Duvernoy, 1842:37–41. Type species *Brachysorex brevicaudus* Duvernoy (=*Sorex brevicaudus* Say), by original designation.

Talposorex Pomel, 1848:248. Type species *Talposorex platyurus* Pomel (=*Sorex brevicaudus* Say), by original designation.

Anotus Wagner, 1855:550–551. Type species *Sorex carolinensis* Bachman, by original designation.

CONTEXT AND CONTENT. Order Insectivora, Family Soricidae, Subfamily Soricinae, Tribe Blarinini (Repenning, 1967). The genus *Blarina* includes three species. Key characters used herein were adapted primarily from George et al. (1981, 1982) but with modification based on data presented by Braun and Kennedy (1983), Genoways and Choate (1972), Moncrief et al. (1982), and Tate et al. (1980).

1 Size large (total length usually greater than 110 mm; occipito-premaxillary length (Choate, 1972*a*) usually greater than 20.5 mm if east of Mississippi River, usually greater than 21.5 if west of Mississippi River); karyotype 2n = 48 to 50, FN = 48 ____ *B. brevicauda*
Size smaller (total length usually less than 110 mm; occipito-premaxillary length usually less than 20.0 mm if east of Mississippi River, usually less than 21.5 if west of Mississippi River); karyotype other than indicated above ____ 2

2 (1) Size smallest in genus (cranial breadth as small as 9.6 mm, usually less than 11.0); karyotype 2n = 50 to 52, FN = 52 (in the subspecies *B. c. peninsulae*) or 2n = 46, 39, 38, or 37, FN = 45 or 44 (in *B. c. carolinensis*) ____ *B. carolinensis*
Size larger (cranial breadth as great as 12.2 mm, usually greater than 10.5); karyotype 2n = 52, FN = 60 to 62 ____ *B. hylophaga*

Blarina brevicauda (Say, 1823)

Northern Short-tailed Shrew

Sorex brevicaudus Say, 1823:164. Type locality west bank of Missouri River, approximately 2 mi E Ft. Calhoun, formerly Engineer Cantonment, Washington Co., Nebraska (Jones, 1964: 68).

Blarina brevicauda: Baird, 1858:42; first use of current name combination.

Sorex talpoides Gapper, 1830:202. Type locality between York and Lake Simcoe, Ontario.

Sorex dekayi Bachman, 1837:377. Type locality New Jersey. The nomenclatorial history of this name and "*Sorex dekayi* De Kay" were reviewed by Handley and Choate (1970).

Galemys micrurus Pomel, 1848:249. A new name proposed for "*Sorex dekayi* De Kay" (Handley and Choate, 1970).

Blarina angusticeps Baird, 1858:34. Type locality Burlington, Chittenden Co., Vermont. Regarded by Merriam (1895) as based on a deformed skull (Bole and Moulthrop, 1942).

Blarina costaricensis J. A. Allen, 1891:205–206. Type locality supposedly La Carpintera, Costa Rica, but assumed by Merriam (1895) to have been somewhere in Upper Mississippi Valley, probably Iowa (Allen, 1897; Bole and Moulthrop, 1942).

Blarina telmalestes Merriam, 1895:15. Type locality Lake Drummond, Dismal Swamp, Norfolk Co., Virginia.

Blarina simplicidens Cope, 1899:219. Type locality Port Kennedy Cave (a pre-Wisconsinan local fauna), Montgomery Co., Pennsylvania.

Blarina brevicauda ozarkensis Brown, 1908:170. Type locality Conard Fissure (a pre-Wisconsinan local fauna), Newton Co., Arkansas. Elevated to specific rank by Graham and Semken, 1976:434.

Blarina fossilis Hibbard, 1943:238. Type locality Rezabek gravel pit (a pre-Wisconsinan local fauna), Lincoln Co., Kansas.

CONTEXT AND CONTENT. Context is given above in the generic account. Eleven Recent subspecies of *B. brevicauda* (exclusive of *B. carolinensis* and *B. hylophaga*), referable to two semispecies (Jones et al., 1984), currently are recognized (Hall, 1981; Handley, 1979):

B. b. aloga Bangs, 1902:76. Type locality West Tisbury, Martha's Vineyard, Dukes Co., Massachusetts.

B. b. angusta Anderson, 1943:52. Type locality Kelly's Camp, Berry Mountain Brook, near head of Grand Cascapedia River, Gaspe Co., Quebec, about 1,600 ft.

B. b. brevicauda (Say, *in* Long, 1823:164), see above.

B. b. churchi Bole and Moulthrop, 1942:109. Type locality Roan Mountain, Mitchell Co., North Carolina.

B. b. compacta Bangs, 1902:77. Type locality Nantucket, Nantucket Co., Massachusetts.

B. b. hooperi Bole and Moulthrop, 1942:110. Type locality Lyndon, Caledonia Co., Vermont.

B. b. kirtlandi Bole and Moulthrop, 1942:99. Type locality Holden Arboretum, Lake and Geauga counties (the county line bisects the type locality), Ohio.

B. b. manitobensis Anderson, 1947:23. Type locality Max Lake, Turtle Mountains, Manitoba, "latitude a little north of 49th parallel, longitude about 100 degrees west; altitude about 2,100 feet."

B. b. pallida R. W. Smith, 1940:223. Type locality Wolfville, Kings Co., Nova Scotia.

B. b. talpoides (Gapper, 1830:202), see above.

B. b. telmalestes Merriam, 1895:15, see above.

DIAGNOSIS. The Nearctic genus *Blarina* includes the nearly uniformly silver to black (often with brown tips on hairs), short-tailed shrews having five unicuspidate teeth in each upper jaw (Fig. 1). The dental formula is as in the genus *Sorex*: falciform incisor, five unicuspids, the fourth premolar, and three molars in each upper toothrow; procumbent incisor, one unicuspid, the fourth premolar, and three molars in each lower toothrow, total 32 (Choate, 1968, 1970, 1975). The genera *Blarina* and *Sorex* readily can be distinguished externally by the relatively much shorter tail of the former (20% of total length is typical for *Blarina*, whereas more than 40% is usual for *Sorex*). *Blarina* can be distinguished from *Cryptotis* in that the latter lacks one unicuspid (30 total teeth in *Cryptotis*, 32 in *Blarina*; Hall, 1981).

Blarina brevicauda is the largest species in the genus (Genoways and Choate, 1972; George et al., 1981; Graham and Semken, 1976; Moncrief et al., 1982). Its geographic range (Fig. 2) lies north of the ranges of *B. hylophaga* (in the west) and *B. carolinensis* (in the east), from which it usually can be distinguished by its greater size. In southern Iowa, northern Missouri, and northeastern Kansas, however, small individuals of *B. brevicauda* may fall within the range of measurements of *B. hylophaga* (Moncrief et al., 1982). Therefore, the most diagnostic character of *B. brevicauda* is its karyotype: FN = 48, 2n = 48 to 50 (George et al., 1982).

GENERAL CHARACTERS. *Blarina brevicauda* is a relatively large, robust shrew (Fig. 3). Its external ears are inconspicuous and concealed by pelage and its eyes are minute. The snout

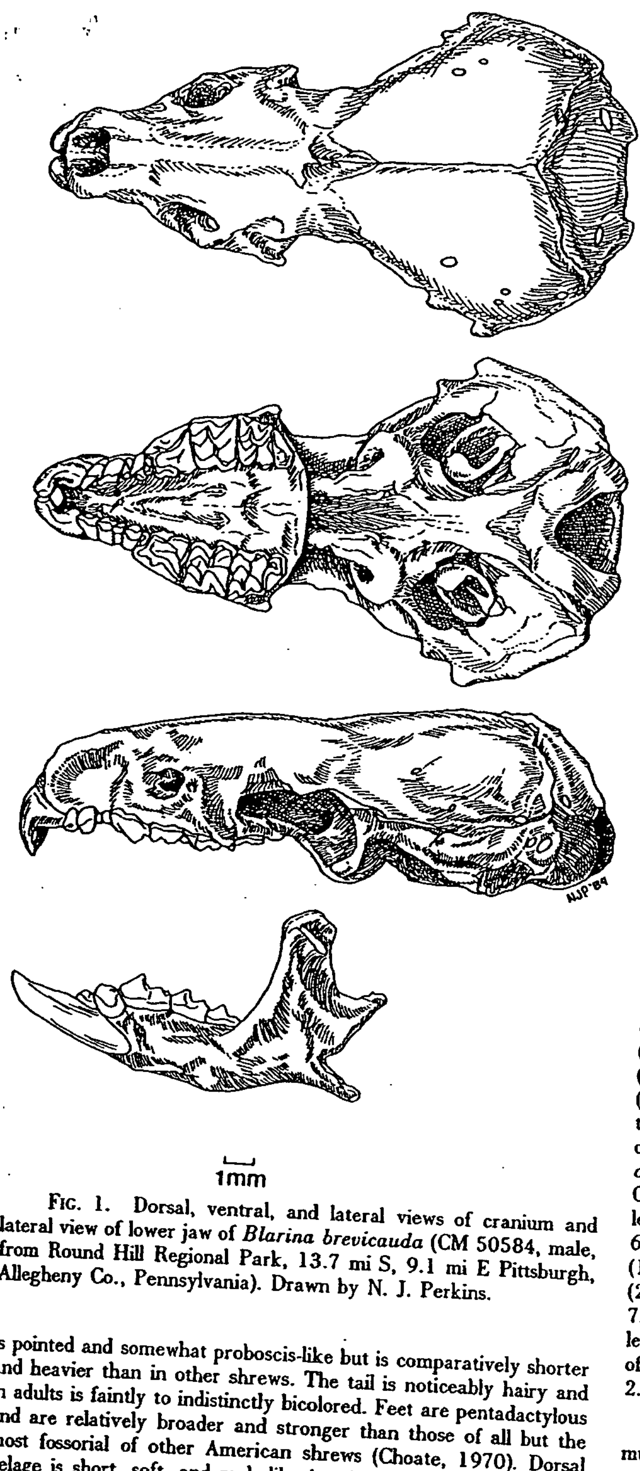

FIG. 1. Dorsal, ventral, and lateral views of cranium and lateral view of lower jaw of *Blarina brevicauda* (CM 50584, male, from Round Hill Regional Park, 13.7 mi S, 9.1 mi E Pittsburgh, Allegheny Co., Pennsylvania). Drawn by N. J. Perkins.

is pointed and somewhat proboscis-like but is comparatively shorter and heavier than in other shrews. The tail is noticeably hairy and in adults is faintly to indistinctly bicolored. Feet are pentadactylous and are relatively broader and stronger than those of all but the most fossorial of other American shrews (Choate, 1970). Dorsal pelage is short, soft, and mole-like in winter, when it often has a dark slate color; ventral pelage sometimes appears paler, at least in part because ventral fur is shorter and denser. Summer pelage is shorter and slightly paler than winter pelage and sometimes is nearly indistinguishable from the short, fuzzy, juvenal pelage. The skull is more massive and angular (Fig. 1) than those of other American shrews and is characterized (in adults) by prominent ridges and processes (Jackson, 1961:43). Teeth are pigmented (deep chestnut in color) and exhibit a relatively unspecialized soricid configuration: "first upper incisors incumbent with tips curved or hooked ventrad and . . . possessing a 2nd . . . unicuspidlike conule . . . ; all other incisors, canines, and all [but the fourth] premolars . . . unicuspid; crowns of upper molars W-shaped" (Hall, 1981:24). Other dental and mandibular characters of shrews were described and illustrated by Repenning (1967).

Nestling short-tailed shrews grow rapidly, and they attain essentially adult size (but not necessarily mass; Dapson, 1968) before they become susceptible to trapping (Guilday, 1957). Accordingly, most authors have opted to disregard variation with age in analyses of morphometric variation (Choate, 1972*a*). Certain authors (Baumgardner and McPherson, 1985; Guilday, 1957; Jackson, 1961) have asserted that males average slightly larger than females in external, cranial, and postcranial measurements, whereas others (Choate, 1972*a*) have found little or no secondary sexual variation in the species.

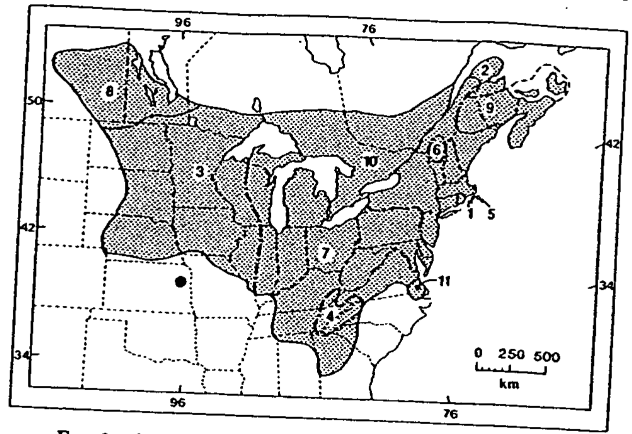

FIG. 2. Map showing the geographic range of *Blarina brevicauda*. Subspecies are: 1, *B. b. aloga*; 2, *B. b. angusta*; 3, *B. b. brevicauda*; 4, *B. b. churchi*; 5, *B. b. compacta*; 6, *B. b. hooperi*; 7, *B. b. kirtlandi*; 8, *B. b. manitobensis*; 9, *B. b. pallida*; 10, *B. b. talpoides*; 11, *B. b. telmalestes*. The dot in northeastern Kansas represents an apparently isolated population of *B. b. kirtlandi*.

Ranges and means (in parentheses) of selected external and cranial measurements (in mm) of samples from Nebraska (Jones, 1964), Iowa (Bowles, 1975), Illinois (Ellis et al., 1978), Pennsylvania (males only, Guilday, 1957), and Connecticut (males only, Choate, 1972*a*) are as follows: total length, 125 to 141 (132.4), 120 to 138 (125.3), ———, 106 to 126 (117.2), ———; length of hindfoot, 16 to 18 (17.0), 14 to 17 (15.8), ———, 13 to 15 (14.0), ———; cranial breadth, 12.8 to 14.0 (13.5), 12.3 to 13.8 (13.1), 11.5 to 12.6 (12.1), 11.8 to 13.4 (12.5), 11.9 to 13.2 (12.6); maxillary breadth, 8.2 to 9.1 (8.7), 8.2 to 8.8 (8.5), 7.3 to 8.0 (7.6), 7.0 to 8.4 (7.8), 7.2 to 8.1 (7.7). Ranges and means of cranial measurements (in mm) of 25 specimens of *B. b. brevicauda* from Nebraska and 23 specimens of *B. b. kirtlandi* from Ohio (Moncrief et al., 1982) are as follows: occipito-premaxillary length, 23.1 to 25.2 (24.0), 20.8 to 23.0 (21.5); P4–M3 length, 6.3 to 6.8 (6.6), 5.6 to 6.0 (5.9); cranial breadth, 12.6 to 14.0 (13.5), 11.5 to 12.6 (12.0); breadth of zygomatic plate, 2.3 to 3.1 (2.7), 2.0 to 2.6 (2.3); maxillary breadth, 8.0 to 9.1 (8.7), 7.1 to 7.8 (7.6); interorbital breadth, 5.9 to 6.7 (6.2), 5.3 to 5.8 (5.5); length of mandible, 13.3 to 14.4 (13.8), 11.6 to 13.0 (12.1); height of mandible, 7.4 to 8.2 (7.9), 6.3 to 7.1 (6.6); articular breadth, 2.8 to 3.2 (3.0), 2.3 to 2.7 (2.4).

DISTRIBUTION. *Blarina brevicauda* occurs throughout much of the north-central and northeastern United States and southern regions of adjacent Canadian provinces (Fig. 2). Marginal records were identified by Hall (1981), but he regarded *B. carolinensis* as only subspecifically distinct from *B. brevicauda*, *B. hylophaga* as a synonym of *B. carolinensis*, and *B. b. telmalestes* as a distinct species. The distribution of *B. brevicauda* overlaps with that of *B. hylophaga* in southern Iowa, northern Missouri, northeastern Kansas, and possibly southeastern Nebraska (Moncrief et al., 1982), and with that of *B. carolinensis* in central Tennessee (Braun and Kennedy, 1983), southern Illinois (Ellis et al., 1978), eastern Virginia (Tate et al., 1980), western North Carolina and Georgia, and eastern Alabama (French, 1981).

FOSSIL RECORD. *Blarina brevicauda* or an ancestral species probably arose from the blarinine stem in the middle or late Pliocene. The earliest record of the genus is represented by specimens of the *talpoides* semispecies of *B. brevicauda* from late Blancan (early Pleistocene) faunas in Kansas. The *brevicauda* semi-

FIG. 3. Photograph of a feeding *Blarina brevicauda*. Photograph by Roger W. Barbour.

species of *B. brevicauda* appeared later in the early Pleistocene, perhaps during the Kansan glacial, but before the origin of the two other species of *Blarina* (*B. carolinensis* in the mid-Irvingtonian and *B. hylophaga* after the Wisconsinan glaciation). Continuity of gene flow between the two semispecies of *B. brevicauda* during the Pleistocene and Holocene and the absence of fixed chromosomal differences between the semispecies apparently prevented speciation of these phena (Jones et al., 1984).

FORM. Merriam (1895:11) described the pelage of *B. brevicauda* as "sooty-plumbeous above, becoming ashy-plumbeous below, varying with the light." Findley and Jones (1956) described three molts. The first, postjuvenal molt does not occur until the shrew is essentially of adult size. The fuzzy juvenal pelage sheds initially in the head region and proceeds caudad; the new pelage (whether long, silky winter fur or shorter summer fur) is determined by the time of year in which the shrew is born. Molt from summer to winter pelage proceeds in a tail-to-head direction in both first- and second-year animals and most often is seen in October and November. Spring molt can occur at any time between February and July; in females it is in a head-to-tail direction, whereas in males it is more irregular (Findley and Jones, 1956). Albinistic *Blarina* have been reported from Delaware, Indiana, New York, Pennsylvania, Vermont (Williams, 1962), and Ohio (Svendson and Svendson, 1975).

Blarina brevicauda possesses three dermal scent glands, one ventral and one on each flank. Sweat glands seem to be the principle component of the lateral glands, whereas sebaceous tissue is more pronounced in the ventral gland (Pearson, 1946). Scent glands are well developed in both males and females; they increase in size in males concomitant with testicular enlargement in spring and autumn (Eadie, 1938) and become smaller in females during estrus, pregnancy, and lactation (Pearson, 1946). Eadie (1938) suggested that scent glands might serve as a means of protection; the musky odor they produce is distasteful to many carnivores, and the abdominal skin is associated closely with the underlying muscles, possibly to facilitate secretion when a shrew becomes excited or upset. The glands also might be used for marking territories, thus serving to separate shrews at times other than during the breeding season (Pearson, 1946); however, the sense of smell is considered to be poorly developed (Schwartz and Schwartz, 1981).

The eye of *B. brevicauda* is degenerate (Gaughran, 1954; Ryder, 1890). It and the optic nerve are diminutive and, although slight motion is possible, the reduced ocular muscles do not arise directly from the skull. Vision probably is limited to perception of light (Schwartz and Schwartz, 1981). The lachrymal gland is much larger than the eyeball, and its duct opens into the conjunctival cavity. The gland has its own investment of striated voluntary muscles, suggesting that the shrew can compress the gland voluntarily, secrete over the eyeball, and wash away dirt that might accumulate there during burrowing activity.

There is controversy about the dental formula of short-tailed shrews. Merriam (1895) described it as i 4/2, c 1/0, p 2/1, m 3/3, total 32. Ārnbāch-Christie-Linde (1912) opined that the dental formula actually is I3, I4, I5, P1, P2, P3, P4, M1, M2, M3/i4, p1, p4, m1, m2, m3, and suggested that two additional rudimentary incisors are present early in embryonic development. Kindahl (1960) found no evidence for these rudimentary incisors and stated that the dental formula is I1, I2, I3, C, P2, P3, P4, M1, M2, M3/i1, i2, p4, m1, m2, m3. James (1963) reinterpreted Kindahl's results and suggested that the dental formula is, in fact, I1, I2, I3, C, P2, P3, P4, M1, M2, M3/i3, c, p4, m1, m2, m3. Choate (1968) described dental abnormalities in *B. brevicauda* and followed James' (1963) interpretation of the dental formula. Because of uncertainty regarding dental homologies, most authors employ the formula given in GENERAL CHARACTERS. Repenning (1967) described the anatomy of individual teeth.

Blarina brevicauda possesses "a pair of extrapulmonary bronchial diverticula emerging from the dorsal caudal margin of the right posterior lobe of the lung," which may be a morphological adaptation to the environment in which the shrews live (Parke, 1956:236). Dust collects in the diverticula, balls up, is ejected into the lungs by the muscular action of the diverticula, and is removed by peristalsis (Parke and Wetzel, 1968).

The ventral aspect of the brain of *B. brevicauda* was figured by Hyde (1959), and the lateral aspect by Le Gros Clark (1932). The secondary optic tracts of the brain are large relative to the primary visual elements (Gillilan, 1941); the optic, oculomotor, trochlear, and abducens nerves are small for mammals and are dwarfed by the trigeminal nerve (Hyde, 1959). With respect to the trigeminus, Hyde (1959:345) stated that *Blarina* "probably represents the greatest reduction in neuronal population that is consistent with adequate brain function." The olfactory tubercle and bulbs are large (Le Gros Clark, 1932). The relative size of the amygdaloid complex is similar to that of other mammals (Crosby and Humphrey, 1944).

The average hematocrit for *B. brevicauda* was 45% and the average hemoglobin was 16.5 g/100 ml, well within the range for other mammals. The average red blood cell count was 18 million/mm, very high for mammals, whereas the average white blood cell count of 2,730/mm was low (Doremus and Jaffe, 1964).

Allen (1894:270) commented on the skull and skeleton of *B. brevicauda* and concluded that the "posterior extremity is of low specialization, and one which supports the trunk imperfectly." Gaughran (1954) described and contrasted the osteology and myology of the cranial and cervical regions of *B. brevicauda* and the eastern mole, *Scalopus aquaticus*. He concluded that their crania have similar proportions and features, but that *Blarina* is specialized more for mastication and *Scalopus* more for burrowing.

Testes are situated inside the abdominal cavity; there is no scrotum (Pearson, 1944). Testes in winter vary in length from 2.5 to 3.5 mm, whereas in the breeding season they usually are longer than 9 mm. An erect penis in the breeding season measures about 30 mm, the terminal third to half of which is glans (Martin, 1967; Pearson, 1944). Male accessory reproductive glands include prostate and bulbo-urethral glands (Eadie, 1947). The vagina during estrus is bent in an S-shape (Pearson, 1944). The uterus is bicornuate; the distance from the base of the bladder to the junction of the uterine horns in winter was as little as 2 mm but in the breeding season increased to more than 12 mm (Pearson, 1944). Ovaries are completely enclosed in ovarian capsules and consist primarily of follicles, with relatively few interstitial cells (Pearson, 1944). The chorioallantoic placenta has been described as endotheliochorial in organization (Wimsatt et al., 1973). Females have three pairs of mammae in the groin region (Schwartz and Schwartz, 1981).

FUNCTION. The metabolic rate of *B. brevicauda* is characterized by short periods of activity with intervening periods of inactivity (Pearson, 1947). The pattern is nearly continuous, although there is a distinct tendency for short-tailed shrews to be more active in the early morning (Morrison, 1948). Periods of activity average about 4.5 min (Buckner, 1964). The shrews are active for only 16% of a 24-h period (Martinsen, 1969), the remainder being spent at a lower, resting metabolic rate (Randolph, 1973). Martinsen (1969) hypothesized that this, together with the proclivity of these shrews to eat nearly any source of energy, accounts for the ability of the species to survive in cold-temperature climates. Within the range of 0°C to 25°C, metabolism is inversely proportional to ambient temperature (Randolph, 1973).

Food consumption averages about 0.56 g g^{-1} day^{-1} in *B. brevicauda* (Morrison et al., 1957), whereas oxygen consumption averages about 5.2 cc g^{-1} h^{-1} (Pearson, 1947). Food consumption in winter is about 43% higher than in summer (Randolph, 1973). Calculated values for basal metabolic rate range from 2.18 to 3.4

cc O_2 g^{-1} h^{-1} (Martinsen, 1969; Neal and Lustick, 1973; Pearson, 1947). Because of its high evaporative water loss, *B. brevicauda* requires free water even though it derives free water from food and metabolic water from oxidation of food (Chew, 1951). Jackson (1961) illustrated and described shrew feces as being about 2.5 cm long, dark green in color, and twisted into a corkscrew shape.

Computed from oxygen consumption, the thermoneutral zone of *B. brevicauda* extends from 25°C to 33°C. Minimal oxygen consumption occurs at 30°C (Neal and Lustick, 1973). The upper lethal ambient temperature appears to be 35°C, at which no amount of evaporative water loss is effective in reversing hyperthermia. Mean body temperature ranges from 38°C to 38.5°C (Chew, 1951; Doremus, 1965), but body temperature elevates appreciably during periods of activity (Kendeigh, 1945).

The poisonous nature of the saliva of *B. brevicauda* was suspected as early as 1889, and several authors described the serious effects experienced after they were bitten by shrews (Krosch, 1973; Maynard, 1889). The poison is secreted from the submaxillary glands through a duct at the base of the lower incisors; when a short-tailed shrew bites another animal, the toxic saliva probably flows along the groove between the two teeth into the wound (Pearson, 1942). In small mammals, the toxin can lead to death from respiratory failure accompanied by severe peripheral vasodilation (Ellis and Krayer, 1955; Pearson, 1942); DeMeules (1954) also demonstrated a possible anti-adrenalin action of the venom. The toxin is a protein with several histimine-like features (Ellis and Krayer, 1955). The LD_{50} of crudely purified toxin is approximately 3.4 mg/kg in mice and cats and 0.6 to 1.2 mg/kg in rabbits (Ellis and Krayer, 1955). Lawrence (1945) compared shrew venom to snake venom and found that, in its neurotoxic and hemotoxic effects, it is most comparable to elapine venom. She suggested that, in addition to its role in predation, it may aid in the breakdown of protein during digestion. Tomasi (1978) opined that one function of the venom is to stun or paralyze its prey, thereby allowing short-tailed shrews to take advantage of prey even though it might not actually be eaten until later. Martin (1981*a*) described the immobilizing effect of the venom on insects and suggested that the venom facilitates food hoarding by *Blarina*.

Evidence that short-tailed shrews employ echolocation to explore their environment was first presented by Gould et al. (1964). Subsequently, Tomasi (1979) investigated the echolocating ability of *B. brevicauda* by testing the ability of individuals to discriminate between open-ended and closed tubes simulating burrows. Lacking other sensory input, ultrasonic "clicks" emitted by the shrews were used to distinguish between open and closed tubes up to 61 cm in length, and at 30.5 cm this distinction was possible for openings as small as 0.63 cm in diameter and around corners up to 90°. The shrews also could distinguish among different kinds of materials blocking the tubes. Echolocation "clicks" were recorded from 30 to 55 kHz (Gould et al., 1964; Tomasi, 1979).

ONTOGENY AND REPRODUCTION. The breeding season of *B. brevicauda* lasts from early February to September (Christian, 1969; Pearson, 1944). Females in estrus were caught in early January, when sexual maturation of males was only beginning (Christian, 1969); conversely, males in breeding condition were caught in mid-October (Pearson, 1944). Dapson (1968) recorded the capture in February of a short-tailed shrew that must have been born in January or December. Two peaks of breeding, in spring and late summer or early autumn, have been noted (Blair, 1940; Hamilton, 1929). Although Pearson (1944) assumed that there was no postpartum estrus in his captive females, Blus (1971) concluded that evidence from wild-caught shrews was too indirect to conclude that it never occurs. Both authors documented instances of estrus occurring after the death of a litter.

Copulation in *B. brevicauda* lasts as long as 25 min and averages 5 min. The shrews are locked together, probably by "the penis becoming rigid after it has passed around one or more sharp bends in the vagina" (Pearson, 1944:77). Erections were observed in sleeping shrews, and the rigid glans took on a flat, leaf-like appearance in an S-shape, caused partly by erectile tissues and partly by a pair of retractor penis muscles (Gibbs, 1955; Pearson, 1944). During copulation, the female usually is active and drags the inactive male behind her. No postcopulatory plug is formed in the vagina. After copulation, the male had to use his mouth to retract the penis. Twenty or more matings in 1 day were observed; at least six matings/day are required to induce ovulation, which usually occurs from 55 to 71 h after the first copulation and never occurs in the absence of copulation. Receptivity of the female decreases if ovulation has occurred but may last for as long as 1 month if it has not. During pregnancy, the corpora lutea regress (Pearson, 1944). Asdell (1965) suggested that the placenta produces enough progesterone to continue pregnancy.

Gestation lasts 21 or 22 days (Hamilton, 1929; Pearson, 1944). Average litter sizes of "six or seven" (Hamilton, 1929:134), 4.7 (Blus, 1971), and 4.5 (Pearson, 1944) have been reported. Hamilton (1929) described a litter of seven neonates as being naked (except for vibrissae, which averaged 1 mm in length), dark pink, and about "honeybee size," and as having closed eyes and ears. At 2 days, external measurements (in mm) were: total length, 31; length of tail, 4; and length of hindfoot, 4.5; weight averaged 1.34 g. At 4 days of age, they weighed an average of 3.8 g and were 48 mm in total length. At 8 days they weighed 6.2 g and had standard measurements of 61, 9.5, and 9. By that time, hair had appeared but teeth had not yet erupted; the shrews were noted to emit a sucking sound and were able to crawl. At 13 days, the young weighed 9 g and measured 73, 12, 16; sex was discernable by the appearance of mammae in females. At 19 days, the upper incisors had appeared through the gums, weight was 9.9 g, and total length was 91 mm. On day 22, when the last of the litter died, the eyes had not opened although the external ear was prominent. Weaning occurs by 25 days of age (Blus, 1971). Pearson (1944) mentioned a captive female that demonstrated receptivity at 47 days of age and noted that captive males had spermatozoa in their testes, which were nearly of adult size, at 50 days of age. The earliest successful breeding of a male recorded by Pearson (1944) was at 83 days of age; Blus (1971) observed a male to breed successfully at 65 days. *B. brevicauda* born in spring mature more rapidly than those born in autumn, and some breed in the same season in which they are born (Blus, 1971; Dapson, 1968; Pearson, 1944).

In mark and release experiments by Pearson (1945), 6% of the originally marked population was recaptured in the second summer. One wild-caught, captive female lived to at least 30 months of age, and one captive-born male lived 33 months. Blus (1971) studied mortality in a captive colony and found that 11.1% lived more than 1 year. The number of young that survived from birth to weaning was 72.6%. Average minimal survival for females and males was 4.4 and 4.6 months, respectively. Age may be determined from the degree of toothwear, with maximum wear indicating an age of about 18 months (Pearson, 1945).

ECOLOGY. Earthworms (Oligochaeta) (Mumford and Whitaker, 1982; Whitaker and Ferraro, 1963) or millipedes (Diplopoda) (Linzey and Linzey, 1973) make up a major portion of the diet of *B. brevicauda*. Hamilton (1941) analyzed 460 stomachs and found that the majority contained insects and annelids and that (in decreasing order of frequency) plant material, centipedes (Chilopoda), arachnids, molluscs, and vertebrates also were represented. He asserted that short-tailed shrews were not heavy predators on field mice, as they had the reputation of being (Merriam, 1884). Eadie (1944, 1948) analyzed *Blarina* feces during high and low population cycles of *Microtus pennsylvanicus* and found that, whereas insects predominated in the diet of *B. brevicauda* even when voles were most numerous, the diet included more voles during periods of high vole density than during low vole density. Eadie (1944, 1952) estimated that three shrews consumed 14 to 27 mice per 2.5 ha during the winter months, thereby acting as an effective control on microtine populations. Allen (1938) and Platt and Blakeley (1973) thought that mice might become important in the diet of *Blarina* when insects are relatively unavailable. In addition, *B. brevicauda* reportedly has preyed on *Sorex* (Eadie, 1949; Hamilton, 1940), a young *Lepus americanus* (Rongstad, 1965), a ribbon snake, *Thamnophis* sp. (O'Reilly, 1949), a 60-cm water snake, *Nerodia* sp. (Cope, 1873), and a slimy salamander, *Plethodon glutinosis* (Hamilton, 1930). *Endogone* and other fungi (Diehl, 1939; Whitaker, 1962) sometimes are included in their diet. Short-tailed shrews store food for future use (Hamilton, 1930; Robinson and Brodie, 1982), especially snails (Gastropoda) (Clench, 1925; Ingram, 1942). Martin (1984) found that food-hoarding by short-tailed shrews occurred primarily in autumn and winter although it could be induced in summer by a sudden abundance of prey.

Species predatory on *B. brevicauda* include: owls—*Aegolius acadicus, Asio otus, A. flammeus, Bubo virginianus, Otis asio,*

and *Strix varia* (Choate, 1972*b*; Dexter, 1978; Getz, 1961*c*; Kirkpatrick and Conway, 1947; Mumford and Whitaker, 1982; Pearson and Pearson, 1947; Williams, 1936); hawks—*Buteo lagopus*, *Circus cyaneus*, and *Falco sparverius* (Mumford and Whitaker, 1982); shrikes—*Lanius* sp. (Jackson, 1961); snakes—*Nerodia* sp., *Agkistrodon contortrix*, *Pituophis melanoleucus*, and members of the Crotalinae (Jackson, 1961); felids—*Felis catus* and *F. rufus* (Errington, 1936; Story et al., 1982); canids—*Canis domesticus*, *C. latrans*, *Vulpes vulpes*, and *Urocyon cinereoargenteus* (Andrews and Boggess, 1978; Fowle and Edwards, 1955; Hamilton, 1935; Mumford and Whitaker, 1982); mustelids—*Mustela erminea*, *M. frenata*, *M. vison*, and *Mephitis mephitis* (Hamilton, 1928, 1959; Mumford and Whitaker, 1982); raccoon, *Procyon lotor* (Hamilton, 1936); opossum, *Didelphis virginianus* (Blumenthal and Kirkland, 1976). Shrews also have been discovered in the stomachs of lake trout, *Salvelinus namaycush* (Fowle and Edwards, 1955) and green sunfish, *Lepomis cyanellus* (Huish and Hoffmeister, 1947).

A literature search on parasites of *B. brevicauda* produced 127 citations, most of which were original descriptions of 144 ecto- and endoparasites. Wittrock and Hendrickson (1979) listed 18 helminths that occurred in *B. brevicauda* in Iowa, and Mumford and Whitaker (1982) listed 32 species of ectoparasites and three orders of endoparasites (Nematoda, Trematoda, and Cestoda) that occurred on and in short-tailed shrews in Indiana. Nixon Wilson (pers. comm.), after examining our bibliography, reported that the papers referred to the following ectoparasites: 2 species of Anoplura; 2 Coleoptera (both leptinids); 1 dipteran (a cuterebrid); 25 Siphonaptera; 34 Acari.

Miller and Getz (1977) calculated that short-tailed shrews have broad habitat requirements but were most common in areas with more than 50% herbaceous cover. Conversely, Dueser and Shugart (1979) iterated that short-tailed shrews in eastern Tennessee have a narrow, somewhat specialized niche. Getz (1961*a*) found that food was the limiting factor in wooded habitats; type of vegetation, cover, temperature, and moisture had little effect on local distribution, although shrews avoided areas with little cover and with extremes of temperature and moisture. Pruitt (1953, 1959) suggested that deep litter protected shrews in hardwood forest from temperature and moisture extremes. *B. brevicauda* was the most ubiquitous and abundant of five species of mammals studied in farmstead shelterbelts in southern Minnesota, based on captures in both wooded and unwooded habitats (Yahner, 1982, 1983). *B. brevicauda* moved between shelterbelts more often than other species studied. In Iowa, *B. brevicauda* was associated with big bluestem, *Andropogon gerardi* (Platt, 1975); in Quebec, they occurred primarily in mature deciduous-coniferous forest and secondarily in fields of tall grasses and sedges (Wrigley, 1969). Sinclair et al. (1967) found short-tailed shrews associated with stone walls in relatively dry situations in eastern deciduous forest; they suggested that humidity might be higher near the stone walls than in adjacent microhabitats, thereby enabling short-tailed shrews to inhabit otherwise dry areas. In eastern Tennessee, *Blarina* consistently occupied areas of high stump and log density, hard ground, few shrubs, and dense overstory, and they fed on larval insects found in the stumps and logs (Kitchings and Levy, 1981). The subspecies *B. b. telmalestes* occurs primarily in marshy habitats in and around the Dismal Swamp of Virginia and North Carolina (Handley, 1979).

Platt and Blakeley (1973) investigated the interspecific relationship between *B. brevicauda* and *Sorex cinereus*, and suggested that *Sorex* populations might be somewhat negatively correlated with density of *Blarina*. Hamilton (1940) thought *B. brevicauda* might have an adverse effect on *S. fumeus* populations, but Jameson (1949) found the opposite to be true. Lindeborg (1941) found a positive correlation between fluctuations in *Peromyscus leucopus* and *B. brevicauda*, and Calhoun (1963) found evidence that the presence of *P. leucopus* on the surface of the ground might force shrews to remain underground. Zegers and Ha (1981) postulated that *P. leucopus* used arboreal habitats to minimize competition with *Blarina*. In Iowa, Heideman et al. (1983) found that members of the genus *Peromyscus* reinvaded flooded areas much more quickly than *Blarina*.

Winter mortality of up to 90% of populations of *B. brevicauda* has been documented, probably related to stress from cold (Barbehenn, 1958; Gottschang, 1965; Jackson, 1961). Population density varies from year to year (Jackson, 1961; Platt, 1968), and populations of short-tailed shrews occasionally crash, requiring several years to recover (Ozoga and Verme, 1968). Christian (1963) found that mean adrenal weight was related directly to population size. Brenner et al. (1983) concluded that reproduction in *B. brevicauda* may not be affected adversely by behavioral interaction as it is in microtines. Estimates of population density range from 1.6/ha to nearly 121/ha (Jackson, 1961; Williams, 1936). Estimates of home-range size usually average about 2.5 ha (Blair, 1940, 1941; Buckner, 1966), and the range of each shrew usually overlaps with the range of one or more other shrews. Blair (1940) thought that *B. brevicauda* did not have territories defended from other shrews.

In abandoned strip-mines, *B. brevicauda* is found only in older areas with stable, moist environmental conditions (Jones, 1974; Kirkland, 1976; Wetzel, 1958). After a timbered area is clear-cut, populations of shrews decline abruptly (Kirkland, 1977). Powerline corridors seem to be a dispersal barrier for short-tailed shrews (Schreiber and Graves, 1977). Because shrews are predators, they concentrate DDT residues at levels 10 times those found in *Peromyscus* and *Clethrionomys* (Dimond and Sherburne, 1969). Stehn et al. (1976) found that shrews significantly increased their consumption of arthropods after an area was sprayed with orthene, thus increasing their intake of pesticide residues. Getz et al. (1977) documented concentrations of lead in *Blarina* adjacent to highways.

BEHAVIOR. Martin (1980) described 54 behavioral patterns in captive short-tailed shrews. *B. brevicauda* is a semifossorial mammal with runways usually in the top 10 cm of soil but with some as deep as 50 cm below the soil surface (Hamilton, 1931; Jameson, 1943). Runways usually parallel the surface but occasionally ascend vertically to it (Jameson, 1943). Shrews dig along and through old rotten logs and often use runways of microtines and moles (Hamilton, 1931). Although there is individual variation in digging behavior, shrews generally dig with their front feet and, when enough soil accumulates, kick it from the tunnel entrance with their hindfeet (Rood, 1958). If the distance to the entrance is great enough, shrews do a sideways somersault and push the dirt out with their noses. They dig at a rate of approximately 2.5 cm/min with frequent stops for short naps. Shull (1907) and Brooks (1908) found burrow systems of *B. brevicauda* literally to honeycomb an area. Shrews spend relatively little time on the surface of the ground (Rood, 1958) but have been reported to climb trees (Carter, 1936). Getz (1961*b*) found them to be more active on cloudy days than on sunny or rainy days.

Nests are underground and spherical in shape, and may be lined with vegetation and even fur of meadow voles, *Microtus pennsylvanicus* (Hamilton, 1929; Rapp and Rapp, 1945; Shull, 1907). However, leaves and grass provided by Rood (1958) for his captive shrews were ignored.

During lactation, female shrews constrict the openings of nests and reinforce the nesting materials (Martin, 1982). Activity of females increases during pregnancy and lactation, possibly as the result of increased nutritional needs. Female shrews retrieve their pups by dragging and by a behavior similar to caravanning. The latter, however, involves only the female and one young. All maternal behavior ceases when the young are weaned (Martin, 1982).

Feces rarely are found in the nest (Hamilton, 1929; Rood, 1958; Shull, 1907); they usually are deposited neatly on the side of a runway, outside the entrance to the nest, or, by captive shrews, in the corners of the cage. *B. brevicauda* twitches restlessly when sleeping. The most common position is with the nose and paws tucked under the belly (Rood, 1958). These shrews rarely stay in one position for more than a few minutes and often arouse to yawn, stretch, and clean themselves before going back to sleep. If several familiar individuals share a cage, they sleep together and constantly try to get to the bottom of the pile. Allison et al. (1977) quantified data on sleep in *B. brevicauda*.

Many authors consider *Blarina* to be solitary and unfriendly (Jackson, 1961; Martin, 1981*b*; Shull, 1907). Rood (1958), however, found that the sociability of short-tailed shrews depended greatly on individual dispositions with age and sex playing a lesser role; males and older animals tended to be less friendly than females and younger animals. Disposition also seems to have a bearing on predatory predilections. Some individuals seemed "terrified" of mice put into their cages, others attacked the mice half-heartedly, and some attacked without hesitation. Phillips (1956:543) noted that a shrew first "fastened its teeth just behind the left ear of the vole . . . and began to gnaw at the base of the skull. It required 11 minutes for the shrew to kill its prey, and during that time it was dragged

roughly and rapidly about the cage, as the vole attempted to shake loose." Olsen (1969) analyzed the agonistic behavior of short-tailed shrews and recognized four action patterns and five postures. He suggested that the postures were used in species recognition, thus minimizing the amount of energy wasted in competition for food, space, and social position.

GENETICS. Standard karyotypes of *B. brevicauda* are characterized by a diploid number of 50, 49, or 48 and a fundamental number of 48 (George et al., 1982). Meylan (1967) concluded that variation in diploid numbers is the result of a fission-fusion event between a pair of large acrocentric autosomes and a pair of small acrocentric autosomes. The totally acrocentric diploid number of 50 is most common (Genoways et al., 1977; George et al., 1982), and a diploid number of 48 has been found in only one specimen from central Illinois (Lee and Zimmerman, 1969). The X-chromosome is a large metacentric (Genoways et al., 1977; Meylan, 1967). Genoways et al. (1977) reported the Y-chromosome to be a small acrocentric in *B. b. brevicauda* and *B. b. kirtlandi*, whereas Meylan (1967) reported it to be a small metacentric in *B. b. talpoides*. George et al. (1982) demonstrated that each speciation event in the genus *Blarina* has been accompanied by fixation of chromosomal differences.

Examination (using starch gel electrophoresis) of 18 presumptive loci in individuals of *B. brevicauda* from Massachusetts and Pennsylvania revealed that mean heterozygosity was nil and the percent of loci polymorphic was 11.1 (George, 1984). Brenner and Atno (1983) found seven distinct protein fractions, representing six autosomal genetic traits, in the lens of the eye of *B. brevicauda*.

REMARKS. Based on the revisionary studies of Merriam (1895) and Bole and Moulthrop (1942), the genus *Blarina* was thought to contain two species—*B. brevicauda* and *B. telmalestes*. The latter subsequently was shown by Handley (1979) to be a subspecies of *B. brevicauda*. However, a series of papers published since 1972 (Braun and Kennedy, 1983; French, 1981; Genoways and Choate, 1972; Genoways et al., 1977; George et al., 1981, 1982; Moncrief et al., 1982; Tate et al., 1980) has demonstrated that the genus consists of at least three species—*B. brevicauda*, *B. carolinensis*, and *B. hylophaga*. Moreover, the nominal subspecies *B. carolinensis peninsulae* may represent a fourth species. Finally, the taxon *B. carolinensis shermani* may prove to be an isolated subspecies of *B. brevicauda* or still another species of *Blarina* (Jones et al., 1984).

The generic name *Blarina* is a coined name that has no derivation. The specific epithet is a combination of two Latin words—*brevis* and *cauda*—meaning short tail.

There are literally hundreds of citations that pertain to *B. brevicauda*. We have not been able to include them all here, but have attempted to cite those that give the most complete information or that summarize other authors' work.

LITERATURE CITED

ALLEN, D. L. 1938. Ecological studies on the vertebrate fauna of a 500-acre farm in Kalamazoo County, Michigan. Ecol. Monogr., 8:347-436.

ALLEN, H. 1894. Observations on *Blarina brevicauda*. Proc. Acad. Nat. Sci., Philadelphia, pp. 269-270.

ALLEN, J. A. 1891. Notes on a collection of mammals from Costa Rica. Bull. Amer. Mus. Nat. Hist., 3:203-218.

———. 1897. Additional notes on Costa Rican mammals, with descriptions of new species. Bull. Amer. Mus. Nat. Hist., 9: 31-44.

ALLISON, T., S. D. GERBER, S. M. BREEDLOVE, AND G. L. DRYDEN. 1977. A behavioral and polygraphic study of sleep in the shrews of *Suncus murinus*, *Blarina brevicauda*, and *Cryptotis parva*. Behav. Biol., 20:354-366.

ANDERSON, R. M. 1943. Nine additions to the list of Quebec mammals with descriptions of six new forms. Ann. Rept. for 1942, Provander Soc. Nat. Hist., Canada, pp. 49-62.

———. 1947. Catalogue of Canadian Recent mammals. Bull. Natl. Mus. Canada, 102:1-238.

ANDREWS, R. A., AND E. K. BOGGESS. 1978. Ecology of coyotes in Iowa. Pp. 249-265, *in* Coyotes: biology, behavior, and management (M. Bekoff, ed.). Academic Press, New York, 384 pp.

ÄRNBÄCH-CHRISTIE-LINDE, A. 1912. Der Bau der Soriciden und ihre Beziehungen zu andern Saugetieren. II. Zur Entwicklungsgeschichte der Zahne. Ontogenie. Morpholog. Jahrbuch., 44:201-296.

ASDELL, S. A. 1965. Reproduction and development. Pp. 1-41, *in* Physiological mammalogy (W. V. Mayer and R. G. Van Gelder, eds.). Academic Press, New York, 2:1-326.

BACHMAN, J. 1837. Some remarks on the genus *Sorex*, with a monograph of the North American species. J. Acad. Nat. Sci., Philadelphia, 7:362-402.

BAIRD, S. F. 1858. Mammals. *In* Reports of explorations and surveys, to ascertain the most practicable and economic route for a railroad from the Mississippi River to the Pacific Ocean, 8(part 1):1-757.

BANGS, O. 1902. Descriptions of two new, insular blarinas from eastern Massachusetts. Proc. New England Zool. Club, 3:75-78.

BARBEHENN, K. R. 1958. Spatial and population relationships between *Microtus* and *Blarina*. Ecology, 39:293-304.

BAUMGARDNER, G. D., AND J. M. MCPHERSON. 1985. Intraspecific variability in cranial and post-cranial features of *Blarina brevicauda* in Tennessee. J. Tennessee Acad. Sci., 60:16-20.

BLAIR, W. F. 1940. Notes on home ranges and populations of the short-tailed shrew. Ecology, 21:284-288.

———. 1941. Some data on the home ranges and general life history of the short-tailed shrew, red-backed vole, and woodland jumping mouse in northern Michigan. Amer. Midland Nat., 25:681-685.

BLUMENTHAL, E. M., AND G. L. KIRKLAND, JR. 1976. The biology of the opossum, Didelphis virginiana, in southcentral Pennsylvania. Proc. Pennsylvania Acad. Sci., 50:81-85.

BLUS, L. J. 1971. Reproduction and survival of short-tailed shrews (*Blarina brevicauda*) in captivity. Lab. Anim. Sci., 21:884-891.

BOLE, B. P., JR., AND P. N. MOULTHROP. 1942. The Ohio Recent mammal collection in the Cleveland Museum of Natural History. Sci. Publ., Cleveland Mus. Nat. Hist., 5:83-181.

BOWLES, J. B. 1975. Distribution and biogeography of mammals of Iowa. Spec. Publ. Mus., Texas Tech Univ., 9:1-184.

BRAUN, J. K., AND M. L. KENNEDY. 1983. Systematics of the genus *Blarina* in Tennessee and adjacent areas. J. Mamm., 64:414-425.

BRENNER, F. J., AND D. K. ATNO. 1983. Morphological and eye lens protein characteristics of three species of small mammals. Proc. Pennsylvania Acad. Sci., 57:173-176.

BRENNER, F. J., R. B. KELLY, AND J. KELLY. 1983. Physiological characteristics of three species of small mammals on surface mined lands. Proc. Pennsylvania Acad. Sci., 57:41-44.

BROOKS, F. E. 1908. Notes on the habits of mice, moles, and shrews. West Virginia Univ. Agric. Exp. Sta. Bull., 113:89-133.

BROWN, B. 1908. The Conard Fissure, a Pleistocene bone deposit in northern Arkansas: with a description of two new genera and twenty new species of mammals. Mem. Amer. Mus. Nat. Hist., 9:157-208.

BUCKNER, C. H. 1964. Metabolism, food capacity, and feeding behavior in four species of shrews. Canadian J. Zool., 42: 259-279.

———. 1966. Populations and ecological relationships of shrews in tamarack bogs of southeastern Manitoba. J. Mamm., 47: 181-194.

CALHOUN, J. B. 1963. The social use of space. Pp. 1-187, *in* Physiological mammalogy (W. V. Mayer and R. G. Van Gelder, eds.). Academic Press, New York, 1:1-381.

CARTER, T. D. 1936. The short-tailed shrew as a tree climber. J. Mamm., 17:285.

CHEW, R. M. 1951. The water exchanges of some small mammals. Ecol. Monogr., 21:215-225.

CHOATE, J. R. 1968. Dental abnormalities in the short-tailed shrew, *Blarina brevicauda*. J. Mamm., 49:251-258.

———. 1970. Systematics and zoogeography of Middle American shrews of the genus Cryptotis. Univ. Kansas Publ., Mus. Nat. Hist., 19:195-317.

———. 1972*a*. Variation within and among populations of the short-tailed shrew in Connecticut. J. Mamm., 53:116-128.

———. 1972*b*. Notes on geographic distribution and habitats of mammals eaten by owls in southern New England. Trans. Kansas Acad. Sci., 74:212-216.

———. 1975. [Review of] A manual of mammalogy: with keys

to families of the world, by A. F. DeBlase and R. F. Martin. J. Mamm., 56:281-283.

CHRISTIAN, J. J. 1963. Endocrine adaptive mechanisms and the physiologic regulation of population growth. Pp. 189-353, *in* Physiologic mammalogy (M. V. Mayer and R. G. Van Gelder, eds.). Academic Press, New York, 1:1-381.

———. 1969. Maturation and breeding of *Blarina brevicauda* in winter. J. Mamm., 50:272-276.

CLENCH, W. J. 1925. Snails eaten by shrews. Nautilus, 39:28.

COPE, E. D. 1873. On a habit of a species of Blarina. Amer. Nat., 7:490-491.

———. 1899. Vertebrate remains from Port Kennedy bone deposit. J. Acad. Nat. Sci., Philadelphia, 11:193-267.

CROSBY, E. C., AND T. HUMPHREY. 1944. Studies of the vertebrate telencephalon. III. The amygdaloid complex in the shrew (*Blarina brevicauda*). J. Comp. Neurol., 81:285-305.

DAPSON, R. W. 1968. Reproduction and age structure in a population of short-tailed shrews, *Blarina brevicauda*. J. Mamm., 49:205-214.

DEMEULES, D. H. 1954. Possible anti-adrenalin action of shrew venom. J. Mamm., 35:425.

DEXTER, R. W. 1978. Mammals utilized as food by owls in reference to the local fauna of northeastern Ohio. Kirtlandia, 24:1-6.

DIEHL, W. W. 1939. Endogone as animal food. Science, 90: 442.

DIMOND, J. B., AND J. A. SHERBURNE. 1969. Persistence of DDT in wild populations of small mammals. Nature, 221:486-487.

DOREMUS, H. M. 1965. Heart rate, temperature and respiration rate of the short-tailed shrew in captivity. J. Mamm., 46:424-425.

DOREMUS, H. M., AND J. J. JAFFE. 1964. Hematologic values for the short-tailed shrew, *Blarina brevicauda*. J. Mamm., 45: 648-649.

DUESER, R. D., AND H. H. SHUGART, JR. 1979. Niche patterns in a forest-floor small-mammal fauna. Ecology, 60:108-118.

DUVERNOY, G. L. 1842. Notices pour Servir á la Monographie du Genre Musaraigne. Mag. Anat. Comp. Paléontol., ser. 2, 4:1-48.

EADIE, W. R. 1938. The dermal glands of shrews. J. Mamm., 19:171-174.

———. 1944. The short-tailed shrew and field mouse predation. J. Mamm., 25:359-364.

———. 1947. Homologies of the male accessory reproductive glands in Sorex and Blarina. Anat. Rec., 98:347-354.

———. 1948. Shrew-mouse predation during low mouse abundance. J. Mamm., 29:35-37.

———. 1949. Predation on *Sorex* by *Blarina*. J. Mamm., 30: 308-309.

———. 1952. Shrew predation and vole populations on a localized area. J. Mamm., 33:185-189.

ELLIS, L. S., V. E. DIERSING, AND D. F. HOFFMEISTER. 1978. Taxonomic status of short-tailed shrews (*Blarina*) in Illinois. J. Mamm., 59:305-311.

ELLIS, S., AND O. KRAYER. 1955. Properties of a toxin from the salivary gland of the shrew, Blarina brevicauda. J. Pharmacol. Exp. Therap., 114:127-137.

ERRINGTON, P. L. 1936. Notes on food habits of southern Wisconsin house cats. J. Mamm., 17:64-65.

FINDLEY, J. S., AND J. K. JONES, JR. 1956. Molt of the short-tailed shrew, Blarina brevicauda. Amer. Midland Nat., 56: 246-249.

FOWLE, C. D., AND R. Y. EDWARDS. 1955. An unusual abundance of short-tailed shrews, *Blarina brevicauda*. J. Mamm., 36: 36-41.

FRENCH, T. W. 1981. Notes on the distribution and taxonomy of short-tailed shrews (genus *Blarina*) in the Southeast. Brimleyana, 6:101-110.

GAPPER. 1830. Observations on the quadrupeds found in the district of Upper Canada extending between York and Lake Simcoe, with the view of illustrating their geographical distribution, as well as of describing some species hitherto unnoticed. Zool. J., 5:201-207.

GAUGHRAN, G. R. L. 1954. A comparative study of the osteology and myology of the cranial and cervical regions of the shrew, *Blarina brevicauda*, and the mole, *Scalopus aquaticus*. Misc. Publ. Mus. Zool., Univ. Michigan, 80:1-82.

GENOWAYS, H. H., AND J. R. CHOATE. 1972. A multivariate analysis of systematic relationships among populations of the short-tailed shrew (genus *Blarina*) in Nebraska. Syst. Zool., 21:106-116.

GENOWAYS, H. H., J. C. PATTON, III, AND J. R. CHOATE. 1977. Karyotypes of shrews of the genera *Cryptotis* and *Blarina* (Mammalia: Soricidae). Experientia, 33:1294-1295.

GEORGE, S. B. 1984. Systematics, evolution, and historical biogeography of the Soricinae with special reference to the genus *Sorex*. Unpubl. Ph.D. Dissert., Univ. New Mexico, Albuquerque, 78 pp.

GEORGE, S. B., J. R. CHOATE, AND H. H. GENOWAYS. 1981. Distribution and taxonomic status of *Blarina hylophaga* Elliot (Insectivora: Soricidae). Ann. Carnegie Mus., 50:493-513.

GEORGE, S. B., H. H. GENOWAYS, J. R. CHOATE, AND R. J. BAKER. 1982. Karyotypic relationships within the short-tailed shrews, genus *Blarina*. J. Mamm., 63:639-645.

GETZ, L. L. 1961*a*. Factors influencing the local distribution of shrews. Amer. Midland Nat., 65:67-88.

———. 1961*b*. Responses of small mammals to live-traps and weather conditions. Amer. Midland Nat., 66:160-170.

———. 1961*c*. Hunting areas of the long-eared owl. Wilson Bull., 73:79-82.

GETZ, L. L., L. VERNER, AND M. PRATHER. 1977. Lead concentrations in small mammals living near highways. Environ. Pollut., 13:151-157.

GIBBS, R. H., JR. 1955. The functional anatomy of the penis of the shrew, Blarina brevicauda. Anat. Rec., 121:298-299.

GILLILAN, L. A. 1941. The connections of the basal optic root (posterior secondary optic tract) and its nucleus in various animals. J. Comp. Neurol., 74:367-408.

GOTTSCHANG, J. L. 1965. Winter populations of small mammals in old fields of southwestern Ohio. J. Mamm., 46:44-52.

GOULD, E., N. C. NEGUS, AND A. NOVICK. 1964. Evidence for echolocation in shrews. J. Exp. Zool., 156:19-38.

GRAHAM, R. W., AND H. A. SEMKEN. 1976. Paleoecological significance of the short-tailed shrew (*Blarina*), with a systematic discussion of *Blarina ozarkensis*. J. Mamm., 57:433-449.

GRAY, J. E. 1838. [Untitled paper read to the Zoological Society of London]. Proc. Zool. Soc. London, 1837:123-126.

GUILDAY, J. E. 1957. Individual and geographic variation in *Blarina brevicauda* from Pennsylvania. Ann. Carnegie Mus., 35:41-68.

HALL, E. R. 1981. Mammals of North America. Second ed. John Wiley and Sons, New York, 1:1-600+*90*.

HAMILTON, W. J., JR. 1928. Weasels eat shrews. J. Mamm., 9: 249-250.

———. 1929. Breeding habits of the short-tailed shrew, Blarina brevicauda. J. Mamm., 10:125-134.

———. 1930. The food of the Soricidae. J. Mamm., 11:26-39.

———. 1931. Habits of the short-tailed shrew, Blarina brevicauda (Say). Ohio J. Sci., 31:97-106.

———. 1935. Notes on food of red foxes in New York and New England. J. Mamm., 16:16-21.

———. 1936. The food and breeding habits of the raccoon. Ohio J. Sci., 36:131-140.

———. 1940. The biology of the smoky shrew (*Sorex fumeus fumeus* Miller). Zoologica, 25:473-492.

———. 1941. The foods of small forest mammals in eastern United States. J. Mamm., 22:250-263.

———. 1959. Foods of mink in New York. New York Fish Game J., 6:77-85.

HANDLEY, C. O., JR. 1979. Mammals of the Dismal Swamp: a historical account. Pp. 297-357, *in* The Great Dismal Swamp (P. W. Kirk, Jr., ed.). Univ. Press Virginia, Charlottesville, 427 pp.

HANDLEY, C. O., JR., AND J. R. CHOATE. 1970. The correct name for the least short-tailed shrew (*Cryptotis parva*) of Guatemala (Mammalia: Insectivora). Proc. Biol. Soc. Washington, 83: 195-202.

HEIDEMAN, P. D., J. B. BOWLES, AND K. R. ERICKSON. 1983. Habitat selection by small mammals on the shoreline of a flood control lake in south-central Iowa. Proc. Iowa Acad. Sci., 90: 93-97.

HIBBARD, C. W. 1943. The Rezabek fauna, a new Pleistocene

fauna from Lincoln County, Kansas. Univ. Kansas Sci. Bull., 29:235-247.

HUISH, M. T., AND D. F. HOFFMEISTER. 1947. The short-tailed shrew (*Blarina*) as a source of food for the green sunfish. Copeia, 1947:198.

HYDE, J. B. 1959. A comparative study of certain trigeminal components in two soricid shrews, Blarina brevicauda and Sorex cinereus. J. Comp. Neurol., 107:339-351.

INGRAM, W. M. 1942. Snail associates of *Blarina brevicauda talpoides* (Say). J. Mamm., 23:255-258.

JACKSON, H. H. T. 1961. Mammals of Wisconsin. Univ. Wisconsin Press, Madison, 504 pp.

JAMES, G. T. 1963. Paleontology and nonmarine stratigraphy of the Cuyama Valley Badlands, California. Part 1. Geology, faunal interpretations, and systematic descriptions of Chiroptera, Insectivora, and Rodentia. Univ. California Publ. Geol. Sci., 45:1-154.

JAMESON, E. W., JR. 1943. Notes on the habits and siphonapterous parasites of the mammals of Welland County, Ontario. J. Mamm., 24:194-197.

———. 1949. Some factors affecting the local distribution and abundance of woodland small mammals in central New York. J. Mamm., 30:221-235.

JONES, C. A., J. R. CHOATE, AND H. H. GENOWAYS. 1984. Phylogeny and paleobiogeography of short-tailed shrews (genus *Blarina*). Pp. 56-148, *in* Contributions in Quaternary vertebrate paleontology: a volume in memorial to John E. Guilday (H. H. Genoways and M. R. Dawson, eds.). Spec. Publ., Carnegie Mus. Nat. Hist., 8:1-538.

JONES, G. S. 1974. Notes on the mammals of a strip-mined area in Pike Co., Indiana. Indiana Audubon Quart., 52:19-32.

JONES, J. K., JR. 1964. Distribution and taxonomy of mammals of Nebraska. Univ. Kansas Publ., Mus. Nat. Hist., 16:1-356.

KENDEIGH, S. C. 1945. Body temperatures of small mammals. J. Mamm., 26:86-87.

KINDAHL, M. 1960. Some aspects of the tooth development in Soricidae. Acta Odon. Scan., 17:203-237.

KIRKLAND, G. L., JR. 1976. Small mammals of a mine waste situation in the central Adirondacks, New York: a case of opportunism by Peromyscus maniculatus. Amer. Midland Nat., 95:103-110.

———. 1977. Response of small mammals to the clearcutting of northern Appalachian forests. J. Mamm., 58:600-609.

KIRKPATRICK, C. M., AND C. H. CONWAY. 1947. The winter foods of some Indiana owls. Amer. Midland Nat., 38:755-766.

KITCHINGS, J. T., AND D. J. LEVY. 1981. Habitat patterns in a small mammal community. J. Mamm., 62:814-820.

KROSCH, H. F. 1973. Some effects of the bite of the short-tailed shrew, *Blarina brevicauda*. J. Minnesota Acad. Sci., 39:21.

LAWRENCE, B. 1945. Brief comparison of short-tailed shrew and reptile poisons. J. Mamm., 26:393-396.

LEE, M. R., AND E. G. ZIMMERMAN. 1969. Robertsonian polymorphism in the cotton rat, *Sigmodon fulviventer*. J. Mamm., 50:333-339.

LE GROS CLARK, W. E. 1932. The brains of Insectivora. Proc. Zool. Soc. London, 1932:975-1013.

LESSON, R.-P. 1842. Nouveau tableau du regne animal. Mammiferes. Arthus Bertrand, Paris, 204 pp.

LINDEBORG, R. G. 1941. Fluctuations in the abundance of small mammals in east-central Illinois, 1936-1939. Ecology, 22: 96-99.

LINZEY, D. W., AND A. V. LINZEY. 1973. Notes on food of small mammals from Great Smoky Mountains National Park, Tennessee-North Carolina. J. Elisha Mitchell Sci. Soc., 89:6-14.

MARTIN, I. G. 1980. An ethogram of captive *Blarina brevicauda*. Amer. Midland Nat., 104:290-294.

———. 1981*a*. Venom of the short-tailed shrew (*Blarina brevicauda*) as an insect immobilizing agent. J. Mamm., 62:189-192.

———. 1981*b*. Tolerance of conspecifics by short-tailed shrews (*Blarina brevicauda*) in simulated natural conditions. Amer. Midland Nat., 106:206-208.

———. 1982. Maternal behavior of a short-tailed shrew (*Blarina brevicauda*). Acta Theriol., 27:153-156.

———. 1984. Factors affecting food hoarding in the short-tailed shrew *Blarina brevicauda*. Mammalia, 48:65-71.

MARTIN, R. A. 1967. Notes on the male reproductive tract of *Nectogale* and other soricid insectivores. J. Mamm., 48:664-666.

MARTINSEN, D. L. 1969. Energetics and activity patterns of short-tailed shrews (*Blarina*) on restricted diets. Ecology, 50:505-510.

MAYNARD, C. J. 1889. Singular effects produced by the bite of a short-tailed shrew, Blarina brevicauda. Contrib. Sci., 1:57-59.

MERRIAM, C. H. 1884. The vertebrates of the Adirondack region, northeastern New York. Trans. Linnaean Soc. New York, 2: 1-233.

———. 1895. Revision of the shrews of the American genera Blarina and Notiosorex. N. Amer. Fauna, 10:5-34, 102-107.

MEYLAN, A. 1967. Formules chromosomiques et polymorphisme Robertsonien chez Blarina brevicauda (Say) (Mammalia: Insectivora). Canadian J. Zool., 45:1119-1127.

MILLER, H., AND L. L. GETZ. 1977. Factors influencing local distribution and species diversity of forest small mammals in New England. Canadian J. Zool., 55:806-814.

MONCRIEF, N. D., J. R. CHOATE, AND H. H. GENOWAYS. 1982. Morphometric and geographic relationships of short-tailed shrews (genus *Blarina*) in Kansas, Iowa, and Missouri. Ann. Carnegie Mus., 51:157-180.

MORRISON, P. R. 1948. Oxygen consumption in several small wild mammals. J. Cell. Comp. Physiol., 31:69-96.

MORRISON, P. R., M. PIERCE, AND F. A. RYSER. 1957. Food consumption and body weight in the masked and short-tail shrews. Amer. Midland Nat., 57:493-501.

MUMFORD, R. E., AND J. O. WHITAKER, JR. 1982. Mammals of Indiana. Indiana Univ. Press, Bloomington, 537 pp.

NEAL, C. M., AND S. I. LUSTICK. 1973. Energetics and evaporative water loss in the short-tailed shrew Blarina brevicauda. Physiol. Zool., 46:180-185.

OLSEN, R. W. 1969. Agonistic behavior of the short-tailed shrew (*Blarina brevicauda*). J. Mamm., 50:494-500.

O'REILLY, R. A., JR. 1949. Shrew preying on ribbon snake. J. Mamm., 30:309.

OZOGA, J. J., AND L. J. VERME. 1968. Small mammals of conifer swamp deeryards in northern Michigan. Michigan Acad. Sci. Arts, Letters, 53:37-49.

PARKE, W. W. 1956. Bronchial diverticula in *Blarina brevicauda*. J. Mamm., 37:236-245.

PARKE, W. W., AND R. M. WETZEL. 1968. Bronchial diverticula in short-tailed shrews: pulmonary adaptation to dust-contaminated environment. J. Exp. Zool., 169:197-204.

PEARSON, O. P. 1942. On the cause and nature of a poisonous action produced by the bite of a shrew (*Blarina brevicauda*). J. Mamm., 23:159-166.

———. 1944. Reproduction in the shrew (Blarina brevicauda Say). Amer. J. Anat., 75:39-93.

———. 1945. Longevity of the short-tailed shrew. Amer. Midland Nat., 34:531-546.

———. 1946. Scent glands of the short-tailed shrew. Anat. Rec., 94:615-629.

———. 1947. The rate of metabolism of some small mammals. Ecology, 28:127-145.

PEARSON, O. P., AND A. K. PEARSON. 1947. Owl predation in Pennsylvania, with notes on the small mammals of Delaware County. J. Mamm., 28:137-147.

PHILLIPS, R. S. 1956. Notes on a captive short-tailed shrew. J. Mamm., 37:543.

PLATT, A. P. 1968. Differential trap mortality as a measure of stress during times of population increase and decrease. J. Mamm., 49:331-335.

PLATT, W. J. 1975. The vertebrate fauna of the Cayler Prairie Preserve, Dickinson County, Iowa. Proc. Iowa Acad. Sci., 82: 108-110.

PLATT, W. J., AND N. R. BLAKELEY. 1973. Short-term effects of shrew predation upon invertebrate prey sets in prairie ecosystems. Proc. Iowa Acad. Sci., 80:60-66.

POMEL, A. 1848. Etudes sur les carnassiers insectivores. Pt. 2. Classification des insectivores. Arch. Sci. Phy. Nat. (Geneva), 9:244-251.

PRUITT, W. O., JR. 1953. An analysis of some physical factors affecting the local distribution of the shorttail shrew (*Blarina brevicauda*) in the northern part of the Lower Peninsula of Michigan. Misc. Publ. Mus. Zool., Univ. Michigan, 79:1-39.

———. 1959. Microclimates and local distribution of small mammals on the George Reserve, Michigan. Misc. Publ. Mus. Zool., Univ. Michigan, 109:1–27.

RANDOLPH, J. C. 1973. Ecological energetics of a homeothermic predator, the short-tailed shrew. Ecology, 54:1166–1187.

RAPP, J. L. C., AND W. F. RAPP, JR. 1945. Resting nest of the short-tailed shrew. J. Mamm., 26:307.

REPENNING, C. A. 1967. Subfamilies and genera of the Soricidae. U.S. Geol. Surv. Prof. Paper, 565:1–74.

ROBINSON, D. B., AND E. D. BRODIE, JR. 1982. Food hoarding behavior in the short-tailed shrew *Blarina brevicauda*. Amer. Midland Nat., 108:369–375.

RONGSTAD, O. R. 1965. Short-tailed shrew attacks young snowshoe hare. J. Mamm., 46:328–329.

ROOD, J. P. 1958. Habits of the short-tailed shrew in captivity. J. Mamm., 39:499–507.

RYDER, J. A. 1890. The eye, ocular muscles, and lachrymal glands of the shrew-mole (*Blarina talpoides* Gray). Proc. Amer. Philos. Soc., 28:16–18.

SAY, T. 1823. Account of an expedition from Pittsburgh to the Rocky Mountains performed in the years 1819 and '20, under the command of Major Stephen H. Long. Compiled by Edwin James. 2 vols., Philadelphia.

SCHREIBER, R. K., AND J. H. GRAVES. 1977. Powerline corridors as possible barriers to the movements of small mammals. Amer. Midland Nat., 97:504–508.

SCHWARTZ, C. W., AND E. R. SCHWARTZ. 1981. The wild mammals of Missouri. Univ. Missouri Press and Missouri Dept. Conserv., Columbia, 356 pp.

SHULL, A. F. 1907. Habits of the short-tailed shrew *Blarina brevicauda* (Say). Amer. Nat., 41:495–522.

SINCLAIR, N. R., L. L. GETZ, AND F. S. BOCK. 1967. Influence of stone walls on the local distribution of small mammals. Univ. Connecticut Occas. Papers, Biol. Sci. Ser., 1:43–62.

SMITH, R. W. 1940. The land mammals of Nova Scotia. Amer. Midland Nat., 24:213–241.

STEHN, R. A., J. A. STONE, AND M. E. RICHMOND. 1976. Feeding response of small mammal scavengers to pesticide-killed arthropod prey. Amer. Midland Nat., 95:253–256.

STORY, J. D., W. J. GALBRAITH, AND J. T. KITCHINGS. 1982. Food habits of bobcats in eastern Tennessee. J. Tennessee Acad. Sci., 57:29–32.

SVENDSON, G. E., AND M. G. SVENDSON. 1975. An albino *Blarina brevicauda* from southeastern Ohio. Ohio J. Sci., 75:32.

TATE, C. M., J. F. PAGELS, AND C. O. HANDLEY, JR. 1980. Distribution and systematic relationship of two kinds of short-tailed shrews (Soricidae: *Blarina*) in south-central Virginia. Proc. Biol. Soc. Washington, 93:50–60.

TOMASI, T. E. 1978. Function of venom in the short-tailed shrew, *Blarina brevicauda*. J. Mamm., 59:852–854.

———. 1979. Echolocation by the short-tailed shrew *Blarina brevicauda*. J. Mamm., 60:751–759.

WAGNER, J. A. 1855. Die Säugthiere in Abbildungen nach der Natur, mit Beschreibungen . . . Fortgesetzt von Dr. Johann Andreas Wagner . . . Supplementband. Abtheilung 5: Die Affen, Zahnlüker, Beutelthiere, Hufthiere, Insectenfresser und Handflügler, 810 pp.

WETZEL, R. M. 1958. Mammalian succession on midwestern floodplains. Ecology, 39:262–271.

WHITAKER, J. O., JR. 1962. Endogone, Hymenogaster, and Melanogaster as small mammal foods. Amer. Midland Nat., 67:152–156.

WHITAKER, J. O., JR., AND M. G. FERRARO. 1963. Summer food of 220 short-tailed shrews from Ithaca, New York. J. Mamm., 44:419.

WILLIAMS, A. B. 1936. The composition and dynamics of a beech-maple climax community. Ecol. Monogr., 6:317–408.

WILLIAMS, M. W. 1962. An albino short-tailed shrew from Vermont. J. Mamm., 43:424–425.

WIMSATT, W. A., A. C. ENDERS, AND H. W. MOSSMAN. 1973. A reexamination of the chorioallantoic placental membrane of a shrew, *Blarina brevicauda*: resolution of a controversy. Amer. J. Anat., 138:207–234.

WITTROCK, D. D., AND G. L. HENDRICKSON. 1979. Helminths of shrews, *Blarina brevicauda* and *Sorex cinereus*, in Iowa. J. Parasitol., 65: 985–986.

WRIGLEY, R. E. 1969. Ecological notes on the mammals of southern Quebec. Canadian Field-Nat., 83:201–211.

YAHNER, R. H. 1982. Microhabitat use by small mammals in farmstead shelterbelts. J. Mamm., 63:440–445.

———. 1983. Population dynamics of small mammals in farmstead shelterbelts. J. Mamm., 64:380–386.

ZEGERS, D. A., AND J. C. HA. 1981. Niche separation of *Peromyscus leucopus* and *Blarina brevicauda*. J. Mamm., 62: 199–201.

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TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] Then, this invention aims at offering the new calcium channel antagonist which checks a calcium inflow into a cell.

[Translation done.]

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[The technical field to which invention belongs] this invention is used as therapeutic drugs, such as hypertension, or a reagent for biochemistry research about a new calcium channel antagonist.
[0002]
[Description of the Prior Art] Calcium ion (calcium2+) is participating in regulation of many cell functions, such as metabolism of excitement of a nerve cell, muscular contraction, secretion of hormone or a digestive enzyme, steroidogenesis, sugar, or a lipid, the proliferation of cells, and specialization. Therefore, it is effective to cause various illnesses, if abnormalities arise in the calcium2+ concentration in a cell, and to prepare the calcium2+ concentration in a cell for the medical treatment of the illness. The cell is preparing the regulatory mechanism for controlling the calcium2+ concentration in a cell strictly. The calcium channel which exists in a cell membrane is one of them, and is controlling the inflow into the direct cell of cull SHIUMUION. A calcium channel antagonist checks the calcium ion inflow by the calcium channel.
[0003] The calcium ion inflow inhibitor by the calcium channel is useful as the lead compounds new type, such as medical supplies, for example, an antihypertensive etc. Moreover, there is a use as a reagent for biochemistry research for the elucidation of a communication-of-information mechanism.
[0004] A shrew bites the earthworm used as food and gallops in anesthesia, and although having the habit stored in a kennel is known, it is not clarified about the anesthesia action mechanism and active substance (Tadaaki Imaizumi work, "the various subjects of a deadly poison animal", 17 pages, a data house, 1994).
[0005]
[Problem(s) to be Solved by the Invention] Then, this invention aims at offering the new calcium channel antagonist which checks a calcium inflow into a cell.
[0006]
[Means for Solving the Problem] this invention person etc. found out that the salivary-glands extract of a shrew had the operation which checks a calcium inflow into a cell, and completed this invention.
[0007] That is, this invention offers the calcium channel antagonist which makes the extract of the salivary glands of a shrew an active principle.
[0008]
[Embodiments of the Invention] The extract of this invention extracts the salivary glands of the shrew belonging to a Sorex group, and is obtained by extracting by the organic solvent. As a shrew, meal Echiuroidea, such as an OOASHI shrew, an EZOTO gully rat, a HIMETO gully rat, and a bra RINATO gully rat, is mentioned. As an organic solvent used for extraction, ketones, such as lower alcohols, such as ethanol and a methanol, and an acetone, are mentioned.
[0009] The extract of the salivary glands of the shrew of this invention can be prescribed for the patient taking-orally-wise because of medical treatment, or parenterally. As an internal use agent, it can consider as liquefied tablets, such as solid tablets, such as powder, a granule, a capsule, and a tablet, or a syrup agent, and an elixir agent. Moreover, it can consider as an injection agent, a membrane medication agent, and a medicine for external application as a parenteral administration agent.

[0010] These tablets are manufactured according to a conventional method by adding the manufacture assistant admitted to an active ingredient pharmacology-wise and in tablet study. Furthermore, it is also possible to consider as a durability tablet with well-known technology. When using the manufacture assistant concerned, the loadings of the extract of the salivary glands of the shrew in the calcium channel antagonist of this invention are usually 0.2 - 10 % of the weight preferably 0.1 to 20% of the weight.
[0011] As the above-mentioned manufacture assistant, the suitable component for a tablet according to routes of administration, such as a tablet for internal use (oral agent), a tablet for injection (injection agent), membrane medication agents (buccal, a troche, ** agent, etc.), and medicines for external application (ointment, pasting agent, etc.), is used. For example, if it is in an oral agent and a membrane medication agent an excipient (example: -- starch, a lactose, a crystalline cellulose, a calcium lactate, and magnesium aluminometasilicate --) a silicic acid anhydride, a mannitol, and a binder (for example, hydroxypropylcellulose --) disintegrator (example: -- a carboxymethyl cellulose --), such as a polyvinyl pyrrolidone carboxymethyl-cellulose calcium and a lubricant (stearin acid MAGUNESHIMU example: --) components for a tablet, such as talc, a coating agent (example : hydroxyethyl cellulose), and a corrigent, -- moreover, if it is in an injection agent the

resolvent which can constitute a water injection agent, or a solubilizing agent (example: -- distilled water for injection --) A physiological saline, a propylene glycol, a suspension agent (example : surfactants, such as a polysorbate 80), If components for a tablet, such as pH regulator (example : an organic acid or its metal salt) and a stabilizer, are in a medicine for external application further Components for a tablet, such as a water or oily resolvent or a solubilizing agent (example : alcohol and fatty acid ester), a binder (example : a carboxyvinyl polymer, polysaccharide), an emulsifier (example : surfactant), and a stabilizer, are used.

[0012] The medicine of this invention which has the above-mentioned composition can be manufactured by the method which added a well-known manufacturing method, for example, a method given in the 10th edition tablet general rules of the Pharmacopoea of Japan, or a suitable improvement.

[0013] The dose of the extract concerning this invention is 1-1000mg in the case where an adult is treated as a concentrate, and it is desirable to prescribe this for the patient in 2 - 3 steps per day. This dose can be fluctuated according to a patient's age, weight, and symptom.

[0014]

[Example] Hereafter, an example and the example of an examination explain this invention in detail.

[0015] 15 OOASHI shrews collected in the adjustment Hokkaido Obihiro district of the salivary-glands extract of an example 1. shrew were immediately frozen with dry ice, and it saved at -20 degrees C. The salivary glands after defrosting were extracted, and it mashed with the mortar, it mixed with 70% ethanol 10mL, and maceration was carried out at 4 degrees C for three days. The supernatant liquid was condensed by the bottom rotating evaporator of reduced pressure (40 degrees C or less), and it was obtained 28mg, having used the salivary-glands extract as the white solid-state.

[0016] an example of examination 1. calcium channel prevention activity examination Homo sapiens neuroblastoma cell (IMR-32) -- 10% fetal-calf-serum content DMEM -- the after [cultivation] and 10% wildebeest Ceram V content DMEM -- N6 and O2- a jib -- CHIRIRU adenosine 3' and 5' -- differentiation inducing of the - annular 1 phosphoric acid was moved and carried out to 1mM and the culture medium which did 2.5microM addition of a bromodeoxyuridine for seven days The culture medium of the flask to which the cell adhered was exchanged for 10% fetal-calf-serum content DMEM containing Fura-2AM (acetoxy methyl ester of Fura-2 which are a calcium2+ susceptibility fluorochrome) of 10microM, it placed for 30 minutes into CO2 incubator (5%CO2, 37 degrees C), and the cell was made to incorporate Fura-2AM. Then, it is Kreps about the cell after having exchanged the culture medium for the fetal-calf-serum content DMEM 10%, leaving it at the room temperature for 15 to 30 minutes and making Fura-2 metabolize Fura-2AM. Ringer It suspended by the concentration of 1.1x106 pieces / mL in HEPESU liquid, and poured distributively every [400micro / L] to the cuvette. 4microL addition of was done by using a shrew salivary-glands extract as 2.7mg / 20microLDMSO solution, excitation light (340nm and 380nm) was irradiated by turns after gentle placement for 5 minutes, 500nm fluorescence intensity was measured, and it asked for the ratio (f340/f380). After 1 minute, 15microL addition of the 2M potassium chloride solution was carried out, it was stimulated, f340/f380 were calculated immediately, and the elevation value was made into the calcium inflow value in a cell compared with the value before a stimulus. As a result of comparing this with it of a sample additive-free group, the rate of calcium ion inflow prevention was 80%. The addition at this time was about 1 of extract for one animal/4.

[0017]

[Effect of the Invention] The calcium channel antagonist of this invention shows the calcium inflow inhibitory action to a cell, and has a use as therapeutic drugs, such as hypertension, or a reagent for biochemistry research.

[Translation done.]

TECHNICAL FIELD

[The technical field to which invention belongs] this invention is used as therapeutic drugs, such as hypertension, or a reagent for biochemistry research about a new calcium channel antagonist.

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PRIOR ART

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* NOTICES *

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MEANS

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[0009] The extract of the salivary glands of the shrew of this invention can be prescribed for the patient taking-orally-wise because of treatment, or parenterally. As an internal use agent, it can consider as liquid preparations, such as solid tablets, such as powder, a granule, a capsule, and a tablet, or syrup, and elixir. Moreover, it can consider as the injection, an application-to-mucosa agent, and a medicine for external application as a parenteral administration agent.
[0010] These tablets are manufactured according to a conventional method by adding the manufacture assistant admitted to an active ingredient pharmacology-wise and in pharmaceutics. Furthermore, it is also possible to consider as a durability tablet with well-known technology. When using the manufacture assistant concerned, the loadings of the extract of the salivary glands of the shrew in the calcium channel antagonist of this invention are usually 0.2 - 10 % of the weight preferably 0.1 to 20% of the weight.
[0011] As the above-mentioned manufacture assistant, the suitable component for a tablet according to routes of administration, such as a tablet for internal use (oral agent), a tablet for injection (injection), application-to-mucosa agents (buccal, a troche, suppository, etc.), and medicines for external application (ointment, pasting agent, etc.), is used. For example, if it is in an oral agent and an application-to-mucosa agent an excipient (example: -- starch, a lactose, a crystalline cellulose, a calcium lactate, and magnesium aluminometasilicate --) a silicic acid anhydride, a mannitol, and a binder (for example, hydroxypropylcellulose --) disintegrator (example: -- a carboxymethyl cellulose --), such as a polyvinyl pyrrolidone carboxymethyl-cellulose calcium and a lubricant (stearin acid MAGUNESHIMU example: --) components for a tablet, such as talc, a coating agent (example : hydroxyethyl cellulose), and a corrigent, -- moreover, if it is in the injection the resolvent which can constitute the aquosity injection, or a solubilizing agent (example: -- the water for injection --) A physiological saline, a propylene glycol, the suspension (example : surfactants, such as polysorbate 80), If components for a tablet, such as pH regulator (example : an organic acid or its metal salt) and a stabilizer, are in a medicine for external application further Components for a tablet, such as a water or oily resolvent or a solubilizing agent (example : alcohol and fatty acid ester), a binder (example : a carboxyvinyl polymer, polysaccharide), an emulsifier (example : surfactant), and a stabilizer, are used.
[0012] The medicine of this invention which has the above-mentioned composition can be manufactured by the method which added a well-known manufacturing method, for example, a method given in the 10th edition tablet general rules of the Pharmacopoea of Japan, or a suitable improvement.
[0013] The dose of the extract concerning this invention is 1-1000mg in the case where an adult is treated as a concentrate, and it is desirable to prescribe this for the patient in 2 - 3 steps per day. This dose can be fluctuated according to a patient's age, weight, and symptom.

[Translation done.]

EXAMPLE

[Example] Hereafter, an example and the example of an examination explain this invention in detail.
[0015] 15 OOASHI shrews collected in the adjustment Hokkaido Obihiro district of the salivary-glands extract of an example 1. shrew were immediately frozen with dry ice, and it saved at -20 degrees C. The salivary glands after defrosting were extracted, and it mashed with the mortar, it mixed with 70% ethanol 10mL, and maceration was carried out at 4 degrees C for three days. The supernatant liquid was condensed by the bottom rotating evaporator of reduced pressure (40 degrees C or less), and it was obtained 28mg, having used the salivary-glands extract as the white solid-state.
[0016] an example of examination 1. calcium channel prevention activity examination man neuroblastoma cell (IMR-32) -- 10% fetal-calf-serum content DMEM -- the after [cultivation] and 10% wildebeest Ceram V content DMEM -- N6 and O2- a jib -- CHIRIRU adenosine 3' and 5' -- differentiation inducing of the - annular 1 phosphoric acid was moved and carried out to 1mM and the culture medium which did 2.5microM addition of a bromodeoxyuridine for seven days The culture medium of the flask to which the cell adhered was exchanged for 10% fetal-calf-serum content DMEM containing Fura-2AM (acetoxy methyl ester of Fura-2 which are a calcium2+ susceptibility fluorochrome) of 10microM, it placed for 30 minutes into CO2 incubator (5%CO2, 37 degrees C), and the cell was made to incorporate Fura-2AM. Then, it is Kreps about the cell after having exchanged the culture medium for the fetal-calf-serum content DMEM 10%, leaving it at the room temperature for 15 to 30 minutes and making Fura-2 metabolize Fura-2AM. Ringer It suspended by the concentration of 1.1x106 pieces / mL in HEPESU liquid, and poured distributively every [400micro / L] to the cuvette. 4microL addition of was done by using a shrew salivary-glands extract as 2.7mg / 20microLDMSO solution, excitation light (340nm and 380nm) was irradiated by turns after gentle placement for 5 minutes, 500nm fluorescence intensity was measured, and it asked for the ratio (f340/f380). After 1 minute, 15microL addition of the 2M potassium chloride solution was carried out, it was stimulated, f340/f380 were calculated immediately, and the rise value was made into the calcium inflow value in a cell compared with the value before a stimulus. As a result of comparing this with it of a sample additive-free group, the rate of calcium ion inflow prevention was 80%. The addition at this time was about 1 of extract for one animal/4.

[Translation done.]

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(54)【発明の名称】　カルシウムチャンネル拮抗剤

(57)【要約】
【課題】　細胞へのカルシウム流入を阻害する新規なカルシウムチャンネル拮抗剤を提供する。
【解決手段】　トガリネズミの唾液腺の抽出物を有効成分とするカルシウムチャンネル拮抗剤。
【効果】　上記カルシウムチャンネル拮抗剤は細胞へのカルシウム流入阻害作用を示し、高血圧症等の治療薬または生化学研究用試薬としての用途を有する。

【特許請求の範囲】
【請求項1】　トガリネズミの唾液腺の抽出物を有効成分とするカルシウムチャンネル拮抗剤。
【発明の詳細な説明】
【0001】
【発明の属する技術分野】本発明は新規なカルシウムチャンネル拮抗剤に関し、高血圧症等の治療薬または生化学研究用試薬として用いられる。
【0002】
【従来の技術】カルシウムイオン（Ca^{2+}）は神経細胞の興奮、筋肉の収縮、ホルモンや消化酵素の分泌、ステロイド合成、糖や脂質の代謝、細胞増殖及び分化等、多くの細胞機能の調節に関与している。従って、細胞内のCa^{2+}濃度に異常が起こると種々の疾病を引き起こし、また疾病の治療には細胞内のCa^{2+}濃度を整えることが有効である。細胞は細胞内のCa^{2+}濃度を厳密にコントロールするための調節機構を準備している。細胞膜に存在するカルシウムチャンネルはその1つであり、カルシウムィオンの直接的な細胞内への流入を制御している。カルシウムチャンネル拮抗剤はカルシウムチャンネルによるカルシウムイオン流入を阻害する。
【0003】カルシウムチャンネルによるカルシウムイオン流入阻害物質は新しいタイプの医薬品、例えば血圧降下剤等及びそのリード化合物として有用である。また情報伝達機構の解明のための生化学研究用試薬としての用途がある。
【0004】トガリネズミは餌とするミミズを噛んで麻酔をかけ、巣穴に貯蔵する習性を持つことが知られているが、その麻酔作用機序及び作用物質については明らかにされていない（今泉忠明著、「猛毒動物の百科」、17頁、データ・ハウス、1994年）。
【0005】
【発明が解決しようとする課題】そこで、本発明は、細胞へのカルシウム流入を阻害する新規なカルシウムチャンネル拮抗剤を提供することを目的とする。
【0006】
【課題を解決するための手段】本発明者等は、トガリネズミの唾液腺抽出物が細胞へのカルシウム流入を阻害する作用を持つことを見出し、本発明を完成した。
【0007】すなわち本発明は、トガリネズミの唾液腺の抽出物を有効成分とするカルシウムチャンネル拮抗剤を提供するものである。
【0008】
【発明の実施の形態】本発明の抽出物はＳｏｒｅｘ属に属するトガリネズミの唾液腺を摘出し、有機溶媒で抽出することにより得られる。トガリネズミとしては、オオアシトガリネズミ、エゾトガリネズミ、ヒメトガリネズミ、ブラリナトガリネズミ等の食虫類が挙げられる。抽出に用いる有機溶媒としてはエタノール、メタノール等の低級アルコール、アセトン等のケトン類などが挙げられる。
【0009】本発明のトガリネズミの唾液腺の抽出物は治療のために経口的あるいは非経口的に投与することができる。経口投与剤としては散剤、顆粒剤、カプセル剤、錠剤などの固形製剤あるいはシロップ剤、エリキシル剤などの液状製剤とすることができる。また、非経口投与剤として注射剤、粘膜投与剤、外用剤とすることができる。
【0010】これらの製剤は活性成分に薬理学的、製剤学的に認容される製造助剤を加えることにより常法に従って製造される。更に公知の技術により持続性製剤とすることも可能である。当該製造助剤を用いる場合は、本発明のカルシウムチャンネル拮抗剤中のトガリネズミの唾液腺の抽出物の配合量は通常は０．１～２０重量％、好ましくは０．２～１０重量％である。
【0011】上記製造助剤として、内服用製剤（経口剤）、注射用製剤（注射剤）、粘膜投与剤（バッカル、トローチ、坐剤等）、外用剤（軟膏、貼付剤等）などの投与経路に応じた適当な製剤用成分が使用される。例えば、経口剤および粘膜投与剤にあっては、賦形剤（例：澱粉、乳糖、結晶セルロース、乳酸カルシウム、メタケイ酸アルミン酸マグネシウム、無水ケイ酸、マンニトール）、結合剤（例えばヒドロキシプロピルセルロース、ポリビニルピロリドン等）、崩壊剤（例：カルボキシメチルセルロース、カルボキシメチルセルロースカルシウム）、滑沢剤（例：ステアリン酸マグネシム、タルク）、コーテング剤（例：ヒドロキシエチルセルロース）、嬌味剤などの製剤用成分が、また注射剤にあっては、水性注射剤を構成し得る溶解剤ないし溶解補助剤（例：注射用蒸留水、生理食塩水、プロピレングリコール）、懸濁剤（例：ポリソルベート８０などの界面活性剤）、ｐＨ調整剤（例：有機酸またはその金属塩）、安定剤などの製剤用成分が、さらに外用剤にあっては、水性ないし油性の溶解剤ないし溶解補助剤（例：アルコール、脂肪酸エステル類）、粘着剤（例：カルボキシビニルポリマー、多糖類）、乳化剤（例：界面活性剤）、安定剤などの製剤用成分が使用される。
【0012】上記構成を有する本発明の薬剤は、公知の製造法、例えば日本薬局方第１０版製剤総則記載の方法ないし適当な改良を加えた方法によって製造することができる。
【0013】本発明に係る抽出物の投与量は、濃縮物として成人を治療する場合で1～1000mgであり、これを1日2～3回に分けて投与することが好ましい。この投与量は、患者の年齢、体重および症状によって増減することができる。
【0014】
【実施例】以下、本発明を実施例及び試験例により詳細に説明する。
【0015】実施例1．トガリネズミの唾液腺抽出物の

調整
北海道帯広地方で採集したオオアシトガリネズミ１５頭を直ちにドライアイスで凍結させ、－２０℃で保存した。解凍後唾液腺を摘出し、乳鉢ですりつぶし、７０％エタノール１０ｍＬと混合して３日間４℃で冷浸した。上清を減圧下ロータリーエバポレーター（４０℃以下）で濃縮し、唾液腺抽出物を白色固体として２８ｍｇ得た。

【００１６】試験例１．カルシウムチャンネル阻害活性試験
ヒト神経芽細胞腫細胞（ＩＭＲ－３２）を１０％牛胎児血清含有ＤＭＥＭで培養後、１０％ヌー・セラムＶ含有ＤＭＥＭにN^6，O^2－ジブチリルアデノシン３'，５'－環状一リン酸を１ｍＭ、及びブロモデオキシウリジンを２．５μＭ添加した培地に移して７日間分化誘導した。細胞が付着したフラスコの培地を１０μＭのＦｕｒａ－２ＡＭ（Ca^{2+}感受性蛍光色素であるＦｕｒａ－２のアセトキシメチルエステル）を含む１０％牛胎児血清含有ＤＭＥＭに交換し、CO_2培養器（５％CO_2、３７℃）内に３０分間置いて細胞にＦｕｒａ－２ＡＭを取り込ませた。続いて培地を１０％牛胎児血清含有ＤＭＥＭに交換し、１５から３０分間室温で放置してＦｕｒａ－２ＡＭをＦｕｒａ－２に代謝させた後、細胞をクレブス　リンガー　ヘペス液に１．１×10^6個／ｍＬの濃度で懸濁し、キュベットに４００μＬづつ分注した。トガリネズミ唾液腺抽出物を２．７ｍｇ／２０μＬＤＭＳＯ溶液として４μＬ添加し、５分間静置後に３４０ｎｍと３８０ｎｍの励起光を交互に照射して５００ｎｍの蛍光強度を測定し、その比（ｆ３４０／ｆ３８０）を求めた。１分後に２Ｍ塩化カリウム水溶液を１５μＬ添加して刺激し、直ちにｆ３４０／ｆ３８０を求め、刺激前の値と比べてその上昇値を細胞内カルシウム流入値とした。これを試料無添加群のそれと比較した結果、カルシウムイオン流入阻害率は８０％であった。この時の添加量は１頭分の抽出物の約１／４であった。

【００１７】
【発明の効果】本発明のカルシウムチャンネル拮抗剤は細胞へのカルシウム流入阻害作用を示し、高血圧症等の治療薬または生化学研究用試薬としての用途を有する。